REMARKS

Reconsideration of the rejections set forth in the Office action mailed May 11, 2004 is respectfully requested. Claims 1-17 and 26-28 are currently under examination; claims 18-25 have been withdrawn.

I. The Invention

For the general purpose of clarification, the applicants refer to the illustration of an embodiment of the invention shown in Figures 2A-B. The following description of this embodiment is taken from the specification on page 12, lines 8-29:

"The method, which is illustrated schematically in Figs. 2A-B, employs DNA probes (202,204) prepared from each sample population (e.g. cDNA or genomic DNA libraries), where each probe is labeled with one of two distinguishable labels (206,208), preferably a fluorescent dye, and contains at a terminus one of two "sample identifier" (SID) sequences (210,212), which are able to hybridize with each other. A corresponding library of target sequence clones (214) is prepared, where each clone is attached to a discrete solid surface, e.g. a collection of microbeads (218) or discrete regions on a solid array. Competitive hybridization of the probes to the microbead library is carried out, whereupon probes of the same sequence from two samples hybridize to their complimentary strands on a given region or bead, forming duplexes (220), but with the SID sequences remaining single stranded. *[Note that Figure 2A does not actually show the SID sequences in single stranded form, but depicts them already hybridized either to each other or to a decoder molecule, as described in the following steps:]* The SIDs are then "titrated" by hybridization/ligation (222) of the two types of SIDs from two samples on the same microbead or region. The "remainder" (unhybridized) SID sequences (224) are quantified, preferably via the use of a pair of SID decoder molecules (226,228), which allows the relative abundance of each sequence to be to determined, as the (enhanced) ratio of two fluorescence intensity signals.

As shown in Figs. 2A-B, a 2:1 intensity ratio, which would have been obtained by simply using labeled probes, is enhanced to 3:1. Use of multiply labeled decoders (230, 232) as shown in Fig. 2B, gives even greater enhancement. Flow cytometry analysis can be used to identify and sort DNA clones which are differentially represented in the two samples."

The applicants included in the previous response, filed on January 23, 2004, a similar drawing showing more of the individual steps described above. In that drawing, probe "B" is present at twice the amount of probe "A". Consequently, after competitive hybridization (bottom left side figure) and "titration" of the SID sequences (bottom right side figure), there are two "remainder" SID's (circled) for probe B.

II. Amendments

Claims 1, 2, 8-10, 17, 26 and 27 have been amended for clarity. The amendments are described further, in response to each of the Examiner's objections, in Sections IV and V below.

No new matter is added by any of the amendments.

III. Citation of References

Applicants acknowledge that references listed in the specification which are not included in an Information Disclosure Statement (such as that submitted on 6/24/2003) will not necessarily be considered by the Examiner.

IV. Claim Objections

Each of the items in the Office Action is addressed as follows.

Item 3. Step (a) of claim 1 has been amended as suggested by the Examiner.

The Examiner also suggests that the claim should recite that "said SID sequences are present as single stranded extensions **in** [rather than on] said duplexes". However, the applicants feel that this wording would make the phrase less clear, since a sequence that is "**in** a duplex" would not normally be considered to be "single stranded".

Item 4. Item 4, on page 3 of the Office Action, is assumed to refer to claim 26. The first section of claim 26 has been amended to include the phrase "contacting said reference library with", which is generally in accordance with the Examiner's suggestion.

Again, the applicants feel that the language "single stranded extensions **in** said duplexes" would be less clear than "single stranded extensions **on** said duplexes".

The claim has been amended to recite "exclusive of the first and second SID sequences",

as suggested by the Examiner.

V. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 1, 2, 16, 17, 26 and dependent claims 3-25, 27 and 28 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of the items in the Office Action is addressed individually below.

At the outset, applicants note that many of the items refer to antecedent basis. As stated in the MPEP at §2173.05(c):

> If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. *Ex parte Porter*, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992) ("controlled stream of fluid" provided reasonable antecedent basis for "the controlled fluid").

Item 7. In claim 1, the phrase "the ratio of said first and second probes forming duplexes with said selected sequence", which the Examiner found unclear, has been amended to "the ratio of duplexes formed by the first probe with said selected sequence to duplexes formed by the second probe with said selected sequence".

Similarly, in claim 26, the phrase "the ratio of said first and second probes having a given sequence and forming duplexes" has been amended to "the ratio of said duplexes formed by the first probe to duplexes formed by the second probe having the same sequence...".

Item 8. The Examiner states that, in claim 1, "the selected sequence is not part of the first nucleic acid population or the second nucleic acid population".

The claim states, however, that the "first and second probes are present in relative amounts proportional to the relative abundance of *the selected nucleic acid sequence in the first and second nucleic acid populations*, respectively". Therefore, a clear relationship between the probes, the selected sequence, and the first and second populations is recited in the claim.

Items 9-11. In claims 1 and 26, the abbreviation "SID" refers to "sample ID"; the abbreviation does not have two different meanings. The claims have been amended in various

places to refer to "first and second SID sequences", rather than simply "SID sequences", for additional clarity. For example, in step (b) of claim 1, "unhybridized SID sequences" has been amended to "unhybridized first SID sequences and/or unhybridized second SID sequences".

Items 12-13. The Examiner stated that "a plurality of different-sequence probes" in claim 2 does not have antecedent basis because "claim 1 does not indicate that said first nucleic acid population has a plurality of different-sequence probes".

This item appears to be similar to item 11 in the previous Office Action. There, the Examiner asserted that claim 2 did not further limit claim 1 because "claim 1 only requires a first probe from a first nucleic acid population...and claim 2 requires a plurality of probes derived from said first population".

Claim 1 describes competitive hybridization of two probes complementary to the same sequence (but having different SID sequences) with a reference sequence. Claim 2 is directed to the same process occurring with additional (multiple) reference sequences and multiple, different-sequence sets of first and second probes from the nucleic acid populations.

Claim 2 recites additional elements not explicitly recited in claim 1, as is common for dependent claims. There is nothing in claim 1 that excludes the presence of a plurality of different-sequence probes.

Item 14. Again, claim 2 recites additional elements not explicitly recited in claim 1, as is common for dependent claims. There is nothing in claim 1 that excludes the presence of multiple copies of different sequences in the reference library.

Item 15. The claim phrase addressed in this item is "*different sequences within the library* are attached to spatially distinct solid phase supports..." (claim 2). In view of the emphasized text, it is clear that the "different sequences" referred to are from the reference library.

Item 16. Claim 1, prior to amendment, contained the exact language "unhybridized SID sequences". This language clearly provides antecedent basis for the phrase "each said unhybridized SID sequence" in dependent claim 5. (The phrase has been amended in both claims with this response.) Applicants refer again to MPEP §2173.05(e), cited above.

Item 17. Independent claim 1 as amended recites "unhybridized first SID sequences

and/or unhybridized second SID sequences". This language provides clear antecedent support for the language "each said unhybridized SID sequence" in dependent claim 6.

One skilled in the art would have no trouble understanding what "each said unhybridized SID sequence" in claim 6 refers to. The term "each" clearly and unambiguously refers to each and every unhybridized SID sequence recited in the parent claim, which includes both the unhybridized first SID sequences and the unhybridized second SID sequences.

Item 18. Claim 5 has been amended to recite "a labeled first or second decoder moiety". This language provides antecedent support for the language ("first decoder moieties" and "second decoder moieties") of dependent claim 6.

Item 19. Claim 6 contains the exact language "decoder moieties". This language clearly provides antecedent basis for the phrase "each said decoder moiety" in dependent claim 7.

Item 20. Claim 8 has been amended to recite "said labeled decoder moiety", for consistency with parent claim 5.

Item 21. Claim 9 has been amended to change "decoder label" to "decoder moiety", for consistency with parent claim 8.

Item 22. Claim 10 has been amended to change "fluorescent labels" to "fluorescent dye molecules", for consistency with parent claim 8.

Item 23. Claim 10 contains the exact language "ratio of fluorescent signals". This language clearly provides antecedent basis for the phrase "said ratio of fluorescent signals" in dependent claim 11.

Item 24. Claim 16 recites an additional feature not explicitly recited in claim 2, as is common for dependent claims. There is nothing in claim 1 or 2 that excludes the possibility of the "first and second nucleic acid populations" being "cDNA libraries derived from expressed genes of each of a plurality of sources".

Item 25. Claim 17 has been amended to explicitly recite "different individuals" or "different populations of individuals".

Item 26. Claim 26 has been amended to change "the nucleic acid populations" in step (a) to "the first and second nucleic acid populations".

Item 27. Claim 26 refers to "first and second probes having the same sequence, exclusive of the first and second SID sequences". The Examiner states that it is "unclear what

sequence in said first and second probes can be considered as 'the same sequence'".

The first and second probes are derived from the first and second nucleic acid populations, respectively (as recited in step (b) of claim 26). The claim does not place any restriction on the composition of the first and second nucleic acid populations. There is no reason why first and second probes, derived from these different populations, could not have a sequence in common (which is what one skilled in the art would understand "having the same sequence..." to mean).

Item 28. The phrase in step (i) of claim 26, "the ratio of said first and second probes having a given sequence and forming duplexes", has been amended to "the ratio of said duplexes formed by the first probe to duplexes formed by the second probe having the same sequence, exclusive of the first and second SID sequences", for consistency with the language in step (b) of the claim.

Item 29. In amended claim 26, the term "complementary sequences" is used in reference to sequences in the microparticle-supported reference library, to which the probe sequences hybridize; i.e., step (i) of the claim recites that "said first and second probes competitively hybridize with *complementary sequences* attached to said microparticles in said reference library, thereby forming duplexes". The term "complement of the same sequence" is used in reference to the nucleic acid populations from which the probes were derived; i.e., step (i) also refers to "the ratio of the amount of the *complement of said same sequence* in the first nucleic acid population to the amount of the *complement of said same sequence* in the second nucleic acid population".

As is clear from the context of the claim, as quoted above, the terms do not refer to the same physical molecules, since the "complementary sequences" are from the reference library and the "complement of the same sequence" is from a nucleic acid population being analyzed. (However, the molecules are related in sequence because they are complementary to the same probe molecule.)

Item 30. Claim 26 has been amended to recite, instead of "each unhybridized SID sequence", "each first SID sequence which is not hybridized in step (ii)" and "each second SID sequence which is not hybridized in step (ii)".

Item 31. The Examiner stated that terms such as "a first fluorescent label" and "first

decoder moieties" in claim 26 did not have sufficient antecedent basis.

Claim 26 has been amended to recite: "applying to each first SID sequence which is not hybridized in step (ii), a first decoder moiety having a first fluorescent label, wherein said first decoder moieties are selectively attachable to unhybridized first SID sequences, and applying to each second SID sequence which is not hybridized in step (ii), a second decoder moiety having a second, distinguishable fluorescent label, wherein said second decoder moieties are selectively attachable to unhybridized second SID sequences". Applicants can find no deficiency in antecedent basis in this clause.

Item 32. The Examiner states that the steps of claim 26 "do not indicate that each microparticle has a fluorescent label".

The claim has been amended to emphasize the role of the microparticle supports. A reading of the claim shows that fluorescent labels are attached to decoder moieties, which in turn are attached to SID sequences, which in turn are attached to probes, which are hybridized to reference sequences, which are attached to microparticles. (See also Figure 2B in the specification.) Accordingly, the microparticles bear fluorescent labels after the steps of the method are carried out.

Item 33. Claim 27 has been amended to refer to "said first decoder moiety" and "said second decoder moiety". Parent claim 26 clearly recites "a first decoder moiety" and "a second decoder moiety", therefore providing explicit antecedent basis.

Item 34. Claim 26 recites "a first decoder moiety having a first fluorescent label" and "a second decoder moiety having a second, distinguishable fluorescent label". Dependent claim 28 recites that such a decoder moiety comprises "multiple fluorescent molecules". There is nothing in claim 26 that excludes the embodiment of dependent claim 28; that is, there is nothing in claim 26 that limits the "fluorescent label" to a single molecule, or that excludes the possibility that a moiety which has a "fluorescent label" could comprise "multiple fluorescent molecules". Therefore, there is no inconsistency or lack of antecedent basis in claim 28.

Standards of Definiteness

In accordance with case law, the "test for definiteness is whether those skilled in the art

would understand the bounds of the claim when read in light of the specification." (*e.g.*, *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F2d 870, 27 USPQ2d 1123 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 1100 (1994); *Orthokinetics, Inc. V. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 USPQ2d 1081 (Fed. Cir. 1986)). The applicants submit that the subject matter and bounds of the claims would be clear to one skilled in the art, who would be familiar with concepts such as differential expression analysis, preparation of probes from nucleic acid populations, and competitive hybridization.

In view of the foregoing, the applicants submit that the pending claims comply with the requirements of 35 U.S.C. §112, second paragraph.

VI. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

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